

# Review of Virus Respiratory Infections in the Milwaukee Area, 1955-65

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ALTHOUGH progress continues to be made in our knowledge and understanding of respiratory viruses, these infections still are a major cause of acute infectious diseases today (1-3). A number of excellent surveillance studies have been undertaken in recent years in an attempt to establish the role various viruses play in respiratory infections (4-7). The results of these studies, however, indicate that the incidence of viruses, as a cause of respiratory infections, can vary from 34 to 75 percent of the total cases. These results also indicate that the significance of particular viral agents varies with the particular ecologic environment and the population studied.

Although a systematic surveillance study is essential to establish the true incidence of respiratory viruses in a given locality, attempts to set up such a study in large communities have proved impractical and present many unsurmountable difficulties. Nevertheless, an evaluation of the laboratory findings of a diagnostic program for virus diseases in a large community such as Milwaukee provides a valuable insight into the viral agents causing major outbreaks of acute respiratory infections. Most of the pa-

tients whose serums were referred to us for confirmation of diagnosis had severe infections, complications, or atypical symptoms. An analysis of these findings, therefore, provides an insight into the viral agents which have presented a significant problem to physicians in the Milwaukee area.

## Materials and Methods

The clinical cases in this study are limited to those with respiratory infections of suspected viral origin on which paired serum samples were received in our laboratory from hospitals or physicians in the Milwaukee area.

Each serum was tested with a battery of viral antigens using complement fixation procedures recommended by the National Communicable Disease Center consisting of 0.2 ml. patient's serum, 0.1 ml. commercial antigen, 0.2 ml. complement, and 0.5 ml. sensitized sheep cells. The viral antigens used in the battery included psittacosis, Q fever, lymphocytic choriomeningitis, adenovirus, and the influenzas. Q fever, a rickettsial disease, is included in our regular respiratory series because the disease is known to be endemic to the cattle of the area and consequently we had a special interest in the incidence of infections in human beings. Tests for herpes, *Mycoplasma pneumoniae*, respiratory syncytial viruses, and the parainfluenzas were also performed when requested or indicated. Those patients for whom we could demonstrate a fourfold or greater increase in antibody titers were interpreted as having active infections.

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Those patients with an unchanged antibody titer above 1:64 and compatible clinical symptoms were interpreted as having recent infections, and all other reactions were considered as being of undetermined time.

The strains of influenza prevalent in a given year were established by the hemagglutination-inhibition test according to the procedures recommended by the World Health Organization for the study of influenza.

### Patterns of Respiratory Infections

Although the incidence of specific virus infections varied from year to year, a number of respiratory syndromes have reappeared in certain periods of the year to form a characteristic pattern for the Milwaukee area.

To begin with, in January of each year we usually received numerous reports of the widespread occurrence of a mild upper respiratory infection which usually persisted for several weeks. Most of these infections were characterized by the common cold syndrome, and few were severe enough to require hospitalization. Results of combined clinical and laboratory studies indicated that at least three or four different viral agents may have been active at this time. Positive confirmations have frequently been made of typical adenovirus and parainfluenza infections.

During the years when major outbreaks of influenza have occurred, we usually received word from physicians during the third or fourth week of January indicating that there was a definite change in the clinical picture and that patients were observed who had typical influenza symptoms. This picture usually remained unchanged for 6 to 8 weeks, and the laboratory findings confirmed extensive outbreaks of influenza.

In late March and early April, the incidence of influenza usually subsided and a variety of respiratory infections became prevalent in the community. Laboratory findings indicate that adenovirus and parainfluenza virus infections were the most prevalent respiratory infections at this time, but sporadic cases of psittacosis, respiratory syncytial virus, and Q fever also were encountered.

Throughout the summer, we frequently received reports of a "flu-like" syndrome in the

community. Numerous investigations were made, but no confirmation could be obtained of the occurrence of any virus respiratory agents or infections. A few of these cases of suspected infections, which had been referred to the Wisconsin State Laboratory of Hygiene for confirmation, were shown to be caused by enteroviruses.

Typical syndromes made their appearance in the fall. One, usually a mild laryngotracheitis syndrome, often appeared in mid-October. This syndrome was frequently followed in several weeks by a second syndrome which included a mild upper respiratory infection and an intestinal infection. Few patients received attention by a physician or hospital because most of these infections were mild. Consequently not enough serums from such cases have been received by our laboratory to establish the causative agent.

During late November and throughout December, many cases of primary atypical pneumonia have been encountered during the past 5 years. A limited study in our laboratory in 1966 confirmed that more than 50 percent of these cases were due to Eaton agent.

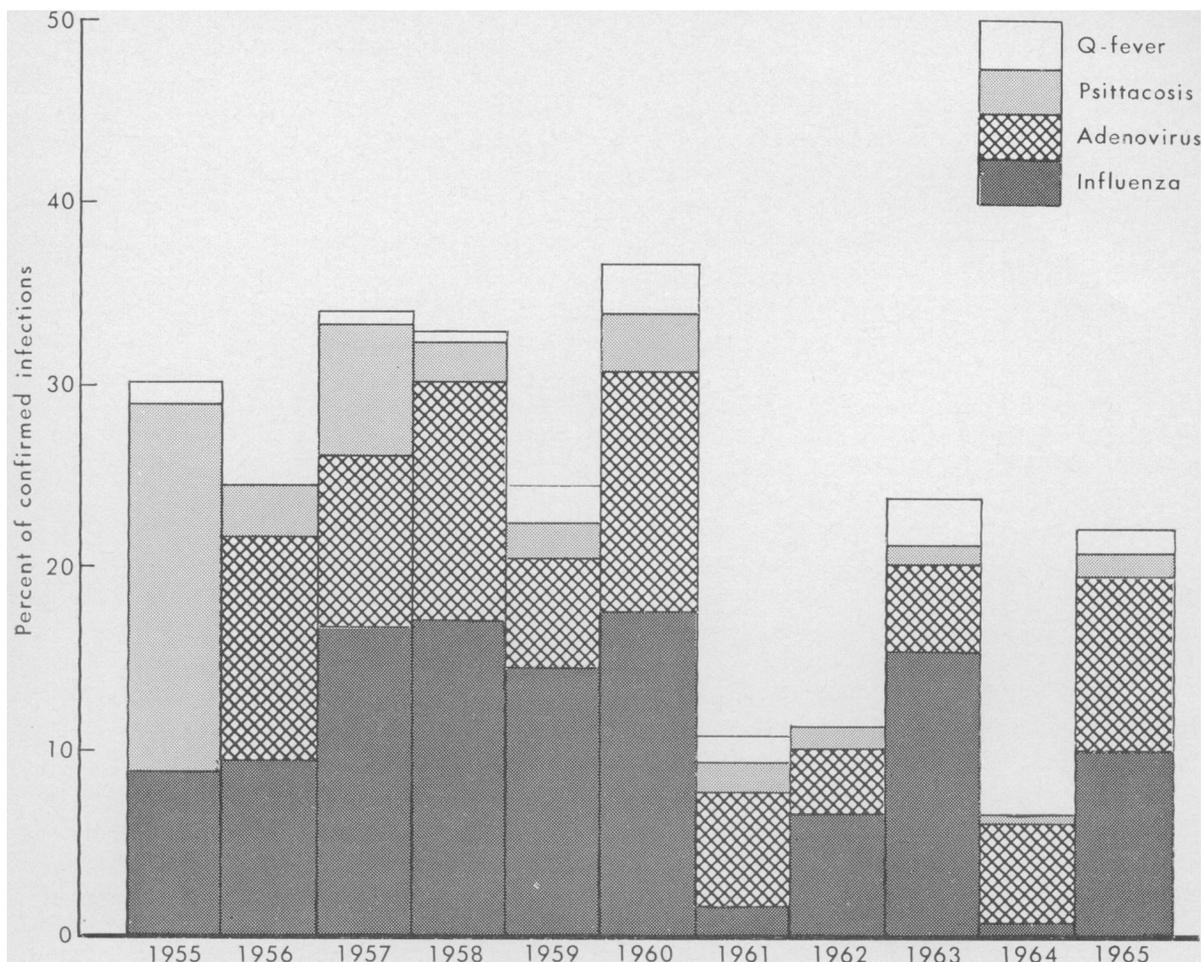
### Respiratory Viruses Studied

A summary of the positive findings on 2,428 paired serums from patients with respiratory diseases of suspected viral origin from 1955 to 1965 is shown in the following table. Positive confirmation of active or recent infection was obtained on 528 (21 percent) of the serums tested.

<i>Virus</i>	<i>Percent positive</i>
Psittacosis -----	2.8
Adenovirus -----	7.7
Q fever -----	1.2
Influenza -----	10.2
Total -----	21.9

A better understanding and appreciation of the role which each agent played in causing acute respiratory infections in the Milwaukee area during this period can be obtained by reviewing the yearly incidence of these diseases, as shown in the chart. Complete data on the results of these studies are given in tables 1 and 2. Several observations on each disease are worthy of note.

## Incidence of confirmed infections of respiratory viruses in Milwaukee area, 1955-65



*Psittacosis.* Extensive occurrence of psittacosis was confirmed in the community in 1955 accounting for 20 percent of our laboratory confirmations. The incidence dropped sharply in 1956 and 1957 and only sporadic cases have appeared since then. The incidence dropped to 3 percent in 1958, and this virus has accounted for less than 2 percent of the positive confirmations since 1960. A total of 202 reactors were encountered during this period; 49 had titers compatible with active infections and 19, with recent infections.

*Q fever.* Although work in our laboratory has demonstrated that Q fever is endemic to cattle of the Milwaukee area, only sporadic infections have been observed in human beings. A total of 103 reactors were encountered during this period, but serums in only 17 cases were indicative of active infections, and in 12, of

recent infections. Most of the infected persons acknowledged contact with infected cattle or with areas contaminated by infected cattle.

*Adenoviruses.* No characteristic pattern could be demonstrated; nevertheless, adenoviruses were encountered in significant numbers each year and have been one of the principal known causes of viral respiratory infections in the Milwaukee area. A total of 371 reactors were encountered, 54 having titers compatible with active infections, 127 with recent infections, and 190 having low unchanged titers indicative of residual antibodies of undetermined time. Extensive occurrence of typical cases of adenoviruses was common immediately preceding and following major outbreaks of influenza. Several institutional outbreaks occurred but remained localized. The incidence of positive confirmations varied from 13.5 percent in 1960

to 3.6 percent in 1962 with an average of 7.7 percent for the entire period.

*Influenza.* The high percentage of confirmations for influenza, 10.2 percent, is representative of the dominant role played by influenza as a major cause of respiratory infections in the Milwaukee area during this period. We wish to emphasize that the cases studied represent merely a small number of the actual total reported in Milwaukee during this period.

Extensive efforts were made to test serums in any suspicious clinical cases whenever influenza was suspected in the community. Once its presence was established, however, only a small representative number were accepted for further confirmation, and studies were limited to severe infections, complications, and atypical clinical cases which presented a problem to the physician. Generally, whenever a physician reported 30 or 40 typical cases, we usually recommended that he select two or three for positive laboratory confirmation.

Thus, although our data indicated that there were only 26 confirmed cases of influenza in 1957, extensive epidemiologic data compiled by Dr. E. R. Krumbiegel, commissioner of health, indicated that there were approximately 120,000 cases in Milwaukee during this outbreak.

Major outbreaks of influenza A2 (Asian) were confirmed in 1958 and 1960 and less severe outbreaks in 1963 and 1965. During this period,

only a single moderate and sporadic outbreak of influenza B was confirmed in 1962. No major outbreaks of influenza A and A1 were encountered and only a few sporadic cases of influenza could be detected in 1961 and 1964.

*Other viruses.* A few typical cases of lymphocytic choriomeningitis were confirmed during this period, but these were sporadic and there was usually a definite association with rodents. Sporadic cases of parainfluenza and respiratory syncytial virus infections usually have occurred in March or April. A significant increase in primary atypical pneumonia has been noted in November during the last 5 years. Limited studies in 1966 indicate that the Eaton agent is a major cause of these infections.

### Significant Outbreaks

*Psittacosis outbreak in 1955.* Numerous typical cases of psittacosis were reported in 1955. Epidemiologic studies revealed that nearly all cases were associated with infected parakeets. Consultation with public health officials disclosed that the difficulty was common throughout the United States and was due to a large influx of parakeets illegally imported from Mexico. The parakeets were being widely distributed through drug and department stores. Vigilant efforts by public health officials and legitimate pet dealers eliminated the infected birds.

**Table 1. Positive laboratory confirmations of respiratory viruses in the Milwaukee area, 1955-65**

Year	Total cases	Psittacosis			Adenovirus			Q fever		
		Active <sup>1</sup>	Recent <sup>2</sup>	Percent of total	Active <sup>1</sup>	Recent <sup>2</sup>	Percent of total	Active <sup>1</sup>	Recent <sup>2</sup>	Percent of total
1955	89	14	4	20.2	0	9	12.3	1	0	1.1
1956	73	2		2.7	0	9	12.3	0	0	0
1957	154	10	1	7.1	8	7	9.7	0	1	.6
1958	184	4	2	3.2	7	17	13.0	1	0	.5
1959	198	3	1	2.0	6	6	6.0	4	0	2.0
1960	288	4	5	3.1	7	32	13.5	4	3	2.4
1961	351	2	4	1.7	4	18	6.2	2	3	1.4
1962	390	4	1	1.3	6	8	3.6	0	0	0
1963	264	2	1	1.1	4	9	4.9	4	3	2.6
1964	205	1	0	.5	7	4	5.3	0	0	0
1965	232	3	0	1.2	5	17	9.5	1	2	1.3
Total	2,428	49	19	2.8	54	127	7.7	17	12	1.2

<sup>1</sup> Fourfold or greater increase in antibody titers.

<sup>2</sup> Unchanged antibody titer above 1:64 and compatible clinical symptoms.

**Table 2. Laboratory confirmations of influenza virus in the Milwaukee area, 1955-65**

Year	Total cases	Active <sup>1</sup>	Percent of total	Strain			
				A	Al	B	Asian
1955	89	8	9.0			<sup>2</sup> 8	
1956	73	7	9.6	6	1		
1957	154	26	16.8				<sup>2</sup> 26
1958	184	32	17.3	1	1		<sup>2</sup> 30
1959	198	29	14.6	<sup>2</sup> 11		9	9
1960	288	50	17.3	13			<sup>2</sup> 37
1961	351	6	1.7			6	
1962	390	26	6.6			<sup>2</sup> 26	
1963	264	41	15.5	1			<sup>2</sup> 40
1964	205	1	.5			1	
1965	232	23	10.3	1	4	1	<sup>2</sup> 18
Total	2,428	250		33	6	51	160

<sup>1</sup> Fourfold or greater increase in antibody titers.

<sup>2</sup> Predominant strain.

Although the parakeet was dominant in the spread of psittacosis in Milwaukee from 1955 to 1958, subsequent studies in our laboratory (8) showed that pigeons have replaced the parakeet as a major source of psittacosis infections in human beings.

*Respiratory syncytial outbreak in 1961.* Although there were few respiratory infections in 1961, late in January we received a report from the pediatric society of an extensive outbreak of croup and bronchiolitis in two major hospitals in the city. Several hundred children were ill at these hospitals, and the outbreak lasted for about 8 weeks. This outbreak was striking because no other cases were reported from the other major hospitals in the city or from the community. Extensive clinical and laboratory studies made in association with Dr. Elaine Thomas, a pediatrician on the staff of both these hospitals, confirmed 17 cases of respiratory syncytial virus and four cases of parainfluenza 1 among 64 cases studied. Tissue culture isolations confirmed that respiratory syncytial virus was the dominant virus in this outbreak.

*Influenza A2 (Asian) outbreaks.* Several aspects of the influenza outbreaks observed in Milwaukee are worthy of note. First, during the outbreak of influenza A2 (Asian) in 1957-58, we observed two waves of infection similar to that reported by Widelock and co-workers in 1958 (9). The first typical clinical cases were observed and positive laboratory confirmations were made late in September 1957. The incidence increased rapidly, spread progressively

throughout the city, peaked in late October, and subsided by mid-November.

A serologic study of the antibody gradient of the random population for Asian influenza was carried on throughout this period. The mean antibody level showed a progressive increase from less than 20 percent in September to 55 percent by the first week in December. The antibody level then declined rapidly, reaching 20 percent by mid-January. During the third week in January, a second extensive outbreak of Asian influenza occurred which lasted until mid-March. The mean antibody level of the random population rose abruptly shortly after the beginning of the second outbreak and remained at a high plateau for many months.

Secondly, even though we received numerous reports of suspected cases of influenza late in January 1965, we could make no confirmation of active infections in the adult population or in hospitalized persons. Finally, reliable reports were received of typical clinical cases in localized outbreaks in a number of schools. A special study was arranged and a positive confirmation made of an extensive localized outbreak among the school children in the affected schools. A confirmation was subsequently made of sporadic infections in the general population.

### Discussion

An evaluation of the results of the diagnostic virology program in the city of Milwaukee from 1955 to 1965 clearly demonstrates the value of

this program to the medical profession and the community. The majority of the 528 cases in which a positive laboratory confirmation was made were either serious infections, complications, or atypical clinical cases which presented a problem to the physician. More important, however, were the laboratory confirmations of significant respiratory outbreaks, particularly those caused by influenza, psittacosis, adenoviruses, and respiratory syncytial viruses.

A review of the respiratory syndromes which have been observed in the community during this time, however, also shows that many difficulties still remain unsolved. Several attempts were made to set up systematic screening of a representative portion of the population to resolve many of the unidentified syndromes and infections. Each time, however, the participants became discouraged because there were no significant respiratory infections during a prolonged period. Such a program would need to continue for at least 2 or 3 years to establish any particular periodicity for the various virus diseases common to a given area.

In spite of these limitations, the program has received extensive praise from the medical profession in the community and is regarded as an excellent complement to the observations previously reported in other communities on surveillance studies of small control groups. This program was possible because the surveillance studies have been confined to a select population in a limited environmental habitat, whereas a large community such as Milwaukee provides a broad ecologic environment with potential reservoirs for numerous virus diseases. The difficulty is further complicated by the tremendous increase in traveling, resulting from improvements in modern travel accommodations. This ease of travel has minimized the barrier of distance that previously existed between large communities and has increased the potentials for the rapid dissemination of infectious diseases. Although the factors which contribute to the cause of widespread outbreaks in a community are not completely understood, constant vigilance is necessary to determine when these outbreaks occur and to attempt to learn the factors which may have contributed to their occurrence.

Specific examples were cited of peculiar out-

breaks of influenza, adenoviruses, and respiratory syncytial viruses which affected hundreds of persons yet would have gone undiagnosed if they had not been called to our attention and if a special effort had not been made to confirm the causal agent. Our knowledge of the part viruses play as the cause of respiratory infections would be greatly enhanced if information were available on the numerous minor respiratory infections which do not reach the physician and hospital and on the unidentified syndromes observed in our community. We sincerely hope that work can be undertaken in the near future to answer some of these problems.

### Summary

Positive confirmation of active or recent infections were obtained for 528 of 2,428 patients in the Milwaukee area with respiratory infections of suspected viral origin from 1955 to 1965. These confirmations included 250 cases of influenza, 10.2 percent; 181 cases of adenovirus infections, 7.7 percent; 68 cases of psittacosis, 2.8 percent; and 29 of Q fever, 1.2 percent. The cases were limited to those in which paired serum samples were sent to our laboratory.

A number of respiratory syndromes have reappeared in certain periods of the year to form a characteristic pattern of respiratory infections for the Milwaukee area. In January mild upper respiratory infections appear that are characterized by the common cold syndrome, and positive confirmations have frequently been made of adenovirus and parainfluenza viruses. In the years that influenza outbreaks occur, typical syndromes are usually reported in the third and fourth weeks of January.

A variety of respiratory infections usually become prevalent in late March and early April. In the summer a "flu-like" syndrome is frequently reported but influenza has not been confirmed. In late November and December many cases of primary atypical pneumonia have appeared in the last 5 years. In 1966 more than 50 percent of these cases were caused by Eaton agent.

Outbreaks which occurred in Milwaukee of particular note included psittacosis in 1955, respiratory syncytial virus in 1961, and influenza A2 (Asian) in 1957-58 and 1965.

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## Recommendations on Medical School Curriculums

At the 79th annual meeting of the Association of American Medical Colleges (AAMC) held in Houston, Tex., October 31-November 4, the membership of the association adopted a recommendation of the executive council proposed by the workshop on medical school curriculum.

The overriding recommendation was that medical schools must actively revise the content and methods used in the total span of the education of the physician so that his professional competence will be most relevant to meeting the changing health needs of the people.

Each of the medical schools was asked to consider the following five specific recommendations.

1. Medical schools must increase their output of physicians. All schools should immediately increase the number of entering students, accelerating expansion by redistributing temporarily the use of existing resources.

2. Medical schools must admit increased numbers of students from geographic areas, economic backgrounds, and ethnic groups that are now inadequately represented.

3. Medical schools must individualize the education of the physician to fit the students' varying rates of achievement, various educational backgrounds, and differing career goals.

4. Medical school curriculums should be developed by interdepartmental groups that

include participation of students. Curriculums should be ratified by the faculty as a body rather than by individual departments.

5. The medical schools must assume a responsibility for education and research in the organization and delivery of health services.

The study of medical school curriculums is one segment of a broader effort by the association to develop explicit policy recommendations which reflect current major trends related to health care and their implications for those responsible for medical education. The data collected for the study were intended to describe more completely the curricular developments currently occurring in the United States and Canada; the mechanisms of change, including how changes were brought about and the factors that inhibited or stimulated changes; the goals of curriculum change; and the direction of evolution of medical curriculums.

The specific goal of the study was to develop a series of recommendations regarding the optimum direction of the future evolution of medical school curriculums, based on an evaluation of the data collected in the perspective of the major problems urgently confronting medical education.

Additional information regarding the study can be obtained by writing directly to the Association of American Medical Colleges, 2530 Ridge Avenue, Evanston, Ill. 60201.